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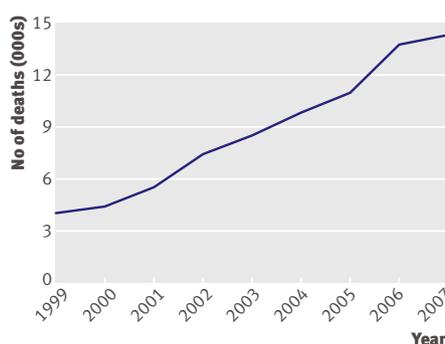
# The prescription opioid crisis

Deaths from prescription opioids tripled in the United States between 1999 and 2007 and are also increasing in many other countries, including the United Kingdom. **Irfan A Dhalla, Navindra Persaud**, and **David N Juurlink** describe ways to reduce morbidity and mortality

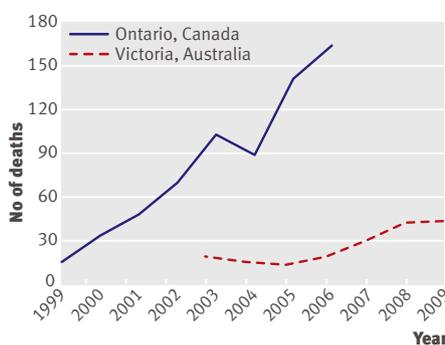
Over the past 25 years, physicians in many countries have become increasingly willing to prescribe opioids for chronic pain with causes other than cancer. The burgeoning use of opioids has been accompanied by a steep increase in opioid related mortality. In the United States, deaths involving opioid analgesics increased from 4041 in 1999 to 14 459 in 2007 (fig 1) and are now more common than deaths from multiple myeloma, HIV, and alcoholic liver disease.<sup>1</sup> Opioid prescribing and opioid related deaths—most of them unintentional and of relatively young people—have also increased elsewhere, including in the United Kingdom. While drug specific data are not universally available, deaths involving oxycodone have increased especially rapidly in several jurisdictions, including Ontario in Canada and Victoria, Australia (fig 2).<sup>2 3</sup>

The International Narcotics Control Board has noted that addiction to prescription opioids is a problem in almost all countries. For example, the board has estimated that between 1.4 million and 1.9 million Germans are addicted to prescription drugs.<sup>5</sup> In the United Kingdom, the former chair of the House of Commons All Party Parliamentary Group on Drug Misuse has expressed concern that the United Kingdom may face a similar epidemic to that of North America in 5 to 10 years, and one doctor has called the increased prescribing of strong opioids for chronic non-cancer pain in the UK a “disaster in the making.”<sup>6</sup> Indeed, deaths involving methadone and codeine roughly doubled in England and Wales between 2005 and 2009, while deaths involving heroin or morphine remained unchanged.<sup>7</sup> Deaths involving tramadol have also become increasingly common in the UK.<sup>7</sup>

In this article, we describe the evolution of the prescription opioid crisis in North America and propose several potential solutions. In addition to reducing morbidity and mortality in countries where the burden of opioid related harm is already high, implementation of these proposals elsewhere could prevent the spread of the crisis to other countries.



**Fig 1** | Deaths involving opioid analgesics in the United States<sup>1 4</sup>



**Fig 2** | Deaths involving oxycodone in Ontario, Canada (data from Dhalla et al<sup>2</sup> updated with coroner's data) and Victoria, Australia (personal communication, Angela Rintoul)

## Rise of opioid related harm

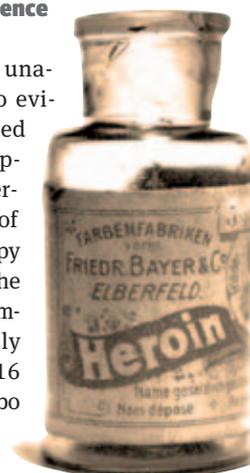
The therapeutic use of compounds derived from the opium poppy predates written history. The first semi-synthetic opioid, diamorphine, was marketed as a cough suppressant by Bayer in 1898. Its proprietary name—heroin—reflected a keen appreciation of its euphoric properties. However, it soon became clear that heroin was rapidly metabolised to morphine and consequently shared all of its associated risks, including addiction, central nervous system depression, and death. In the early part of the 20th century, the morbidity associated with opioids led many countries to pass laws restricting their use. For

example, the United States approved the Harrison Narcotics Tax Act in 1914, making it illegal for physicians to prescribe opioids to treat addiction, and the League of Nations banned heroin outright in 1925. Drug manufacturers responded to these restrictions by synthesising and marketing several new opioids, including oxycodone and hydromorphone. But by the early 1930s, international regulations had been broadened to restrict the sale of all opioids. For the next few decades, opioids were prescribed relatively infrequently.

During the second half of the 20th century, most physicians became comfortable prescribing opioids for acute pain and pain due to cancer. Opioids have improved the quality of life for millions of patients with such pain. In contrast, opioids were rarely prescribed to patients with chronic pain from other causes until the 1980s, when opinion leaders began to advocate their broader use. In the 1990s, coincident with the approval and marketing of several new opioid formulations in North America, the notion that chronic non-cancer pain was under-recognised and undertreated became widespread. By the mid-1990s, the pendulum had swung sufficiently far that physicians reluctant to prescribe opioids for chronic non-cancer pain came to be criticised as being “opiophobic.”<sup>8</sup>

## Marketing in the evidence void

Many physicians are unaware that there is no evidence from randomised controlled trials to support the popular assertion that the benefits of long term opioid therapy outweigh the risks.<sup>9</sup> The trials that have been completed were generally short term (less than 16 weeks) and used placebo comparators (rather than paracetamol or



non-steroidal anti-inflammatory drugs). Furthermore, because these trials invariably excluded patients at high risk of serious adverse events, neither their safety nor efficacy findings can be generalised to everyday clinical practice.<sup>10</sup>

The evidence for the use of opioids in chronic non-cancer pain is sufficiently limited that the authors of one Cochrane review concluded that they should not be used even for severe osteoarthritic pain.<sup>11</sup> A recently published observational study supports the assertion that the risks of opioids outweigh the benefits in this setting.<sup>12</sup> The dearth of high quality evidence has left those who write clinical practice guidelines in the unenviable position of having insufficient evidence with which to formulate meaningful recommendations. As a result, rather than recommending for or against the long term use of opioids, some guidelines merely recommend that physicians “consider the evidence related to effectiveness” before deciding to initiate treatment.<sup>13</sup>

Despite the paucity of evidence, drug manufacturers have aggressively promoted opioids for use in patients with chronic non-cancer pain. The case of OxyContin, a sustained release formulation of oxycodone sold by Purdue Pharma in North America, warrants particular consideration because successful legal proceedings against Purdue and several of its executives have made public many aspects of its marketing.<sup>14 15</sup> In court documents and a United States Congressional investigation, Purdue acknowledged that its employees misled physicians about the risk of addiction. Some Purdue employees suggested that OxyContin could be used to “weed out” addicts and drug seekers,<sup>15</sup> while others capitalised on the prevalent misconception that oxycodone is less potent than mor-

phine<sup>15</sup> when the converse is true. Certain aspects of Purdue’s marketing methods are particularly remarkable in light of the drug’s abuse liability and potential lethality. The manufacturer targeted physicians who prescribed OxyContin frequently, paid its sales representatives large bonuses as an incentive to increase OxyContin sales, and issued coupons entitling new patients to free samples at participating pharmacies.<sup>16</sup>

Other opioid manufacturers have also been cited for inappropriate marketing. For example, Janssen Pharmaceuticals was warned by the US Food and Drug Administration for making false safety claims and unsubstantiated effectiveness claims about its transdermal fentanyl patch.<sup>17</sup> Similarly, the FDA warned King Pharmaceuticals that “the omission of serious and potentially fatal risks” associated with its morphine-naltrexone product was “especially egregious and alarming in its potential impact on the public health.”<sup>18</sup>

### Reducing opioid related harm

Most clinicians acknowledge that opioid related harm is a major public health problem, but there are no universally accepted solutions. Given the scale of the problem—there are more deaths from prescription opioids in North America than from heroin and cocaine combined—we believe an aggressive approach is necessary. We propose several strategies that, if implemented together, could substantially reduce the number of deaths involving opioid analgesics.

### Marketing restrictions

We suggest the abolition of specific marketing practices for prescription drugs with potential for abuse. Drug companies should be prohibited from

linking employee compensation with the volume of opioid prescriptions, and coupons entitling new patients to a free prescription should not be permitted for potentially addictive drugs. Additionally, regulatory authorities should ensure that all promotional material for opioids is accurate and adheres to existing regulations. Regulators should evaluate advertisements before they are deployed rather than simply warning manufacturers after misleading claims have been widely disseminated. Marketing that contravenes policy should be discouraged by a meaningful deterrent, so that companies do not come to view penalties as the cost of doing business. It is worth noting that the \$634m (£387m; €440m) fine given to Purdue for misbranding OxyContin represents substantially less than a single year of the drug’s sales (US sales for 2010 were \$3.5bn<sup>19</sup>).

The ultimate regulatory sanction would be to rescind approval for individual opioid formulations. At least one group with support from people affected by opioid related harm ([www.banoxycontin.com](http://www.banoxycontin.com)) has lobbied the FDA to ban OxyContin. Although this is clearly a radical measure, it may be the only way to effectively counter the durable consequences of Purdue’s illegal marketing. In support of this argument is evidence that OxyContin sales in the United States continued to increase after Purdue’s guilty plea agreement was widely publicised. Although it could be argued that the withdrawal of one opioid would simply lead to increased use of another, the UK experience after the withdrawal of co-proxamol indicates that this might not be the case.<sup>20</sup>

### Patient and physician registries

Many jurisdictions require that physicians who prescribe methadone for opioid addiction, as well as their patients, register with a governmental or quasi-governmental authority. The reasons for this are that methadone toxicity can be fatal, the drug is often sold illegally, and that some patients seek prescriptions from multiple physicians and pharmacies. Each of these observations is also true for other prescription opioids. In our view, the legitimate privacy concerns associated with registries are offset by public health considerations. Registration of high dose or long term treatment for chronic non-cancer pain would allow education to be targeted at physicians who prescribe opioids frequently or at very high doses.<sup>21 22</sup> Setting a dose threshold for registration may also remind physicians that the risk of opioid related mortality in patients with chronic pain is strongly associated with the prescribed dose.<sup>23</sup>

### Real time electronic databases

In some jurisdictions (such as, Kentucky and British Columbia), prescriptions for opioids and other controlled substances are maintained in a



Bayer marketed heroin in 1898 as a cure for morphine addiction and a cough suppressant

centralised database accessible to physicians and pharmacists before they prescribe or dispense a drug. These “real time” electronic databases could make it much harder to obtain opioids from multiple doctors or pharmacies. Real time databases would also help avoid synergistic drug interactions that occur when multiple central nervous system depressants are prescribed and might also strengthen the physician-patient relationship by allowing the physician to verify a patient’s history. Where these databases exist, we believe physicians and pharmacists should be required to access them before prescribing or dispensing opioids.

### Education

Given the attention paid to physicians by drug company representatives,<sup>16</sup> regulatory authorities should consider educational outreach programmes to improve the appropriateness of opioid prescribing.<sup>20</sup> Educational outreach programmes use some of the same marketing principles as the drug industry (such as, face to face meetings, frequent encounters, and concise reading material) but use independent healthcare professionals. Physicians could be educated about the lack of evidence supporting the long term use of opioids for chronic non-cancer pain, the relative potency of commonly used opioids, the potential for dangerous interactions with sedatives and alcohol and how to screen for drug misuse and diversion, as well as the safety, effectiveness and availability of potential alternatives, including paracetamol, non-steroidal anti-inflammatory drugs, antidepressants and non-pharmacologic treatment options.

Most jurisdictions have yet to implement public education campaigns highlighting the potential hazards of prescription opioids, particularly when combined with alcohol or sedatives. Such initiatives should be seriously considered, particularly in light of the effectiveness of public education campaigns aimed at reducing deaths from motor vehicle collisions, melanoma, and alcohol related illness.

### Research

Finally, drug companies and research funding agencies should encourage and support well designed studies to characterise the patient populations that stand to benefit from long term opioid treatment. The FDA and the European Medicines Agency should go further and mandate long term trials to better delineate the circumstances in which the benefits of opioids justify the potential risks. Industry initiated long term clinical trials are a matter of course in oncology and cardiovascular medicine, yet no such trials have been conducted on the use of opioids for chronic non-cancer pain.



## There are more deaths from prescription opioids in North America than from heroin and cocaine combined

### Conclusion

Although opioids are a valuable option for the treatment of acute pain and chronic cancer pain, the risk to benefit ratio is not nearly as clear in patients with non-cancer pain. With more than 1000 deaths every month in the United States, the risks of long term opioid therapy may outweigh the benefits in unselected populations. Maintaining access to opioid analgesics for appropriately selected patients while striving for major reductions in opioid related deaths is a challenging objective that must be a priority in the years ahead.

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